

Method for producing alkoxymalononitriles

The invention relates to a process for preparing alkoxymalononitriles.

- 5 International patent application WO-A-98/31652 describes the preparation of the anesthetic sevoflurane (fluoromethyl 1,1,1,3,3,3-hexafluoro-2-propyl ether) by reacting methoxymalononitrile with bromine trifluoride. However, WO-A-98/31652 does not disclose the preparation of methoxymalononitrile.
- 10 It is accordingly an object of the present invention to provide a process for preparing alkoxymalononitriles.

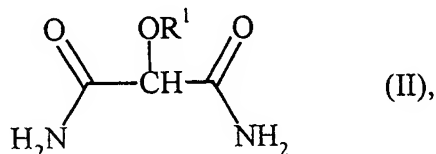
According to the invention, this object is achieved by the process according to claim 1.

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It has been found that alkoxymalononitriles of the general formula



- 20 where R^1 is C_{1-6} -alkyl or halogen-substituted C_{1-6} -alkyl can be prepared by reacting the appropriate alkoxymalonamides of the general formula



- 25 where R^1 is as defined above with a dehydrating agent.

" C_{1-6} -alkyl" are here and hereinbelow all linear or branched alkyl groups having 1-6 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, isopentyl, *tert*-pentyl, neopentyl, hexyl or isohexyl.

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"Halogen-substituted C_{1-6} -alkyl" are C_{1-6} -alkyl groups which are mono- or polysubstituted by halogen. Preferred halogens are fluorine, chlorine and bromine. Particular preference is given to fluorine. Examples include: mono-, di-

or trifluoromethyl, chloromethyl, bromomethyl, 1- or 2-fluoroethyl, 1- or 2-chloroethyl, 1- or 2-bromoethyl and 1-, 2- or 3-fluoropropyl.

The R¹ radical is preferably methyl or trifluoromethyl.

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Examples of useful dehydrating agents include trifluoroacetic anhydride, dibutyltin oxide, phosphorus oxychloride, phosphorus trichloride and phosphorus pentachloride. Preference is given to trifluoroacetic anhydride and phosphorus oxychloride.

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The dehydrating agent is advantageously used in quantities of from 0.5 to 6 molar equivalent per amide group of the alkoxymalonamide of the formula II.

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The dehydration is advantageously carried out in a suitable solvent. Examples of useful solvents include acetonitrile, dioxane, 1,2-dichloroethane, toluene, cyclohexane, heptane and octane. Preference is given to acetonitrile.

Preference is given to carrying out the dehydration in boiling solvent.

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The dehydration is optionally carried out in the presence of a Lewis acid. Examples include the following Lewis acids: BF₃, BCl₃, BBr₃, BI₃, SbF₅, AlCl₃, AlBr₃, TiBr₄, TiCl₄, TiCl₃, ZrCl₄, PF₅, FeCl₃ and FeBr₃.

Preference is given to using AlCl₃ as the Lewis acid.

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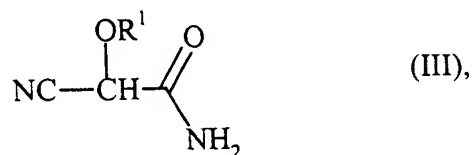
The quantity of Lewis acid is preferably from 0.01 to 0.05 molar equivalent.

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The compounds of the formula II can be prepared by known processes. For example, *Monatsh. Chem.*, 1965, 96, 1677-1689 describes a process for preparing alkoxymalonamides by reacting methyl alkoxyacetates with dialkyl oxalates and reacting the product (dialkyl alkoxymalonate) with liquid ammonia.

The dehydration according to the invention proceeds in two stages, and the intermediate product formed is the corresponding 2-cyano-2-alkoxyacetamide of the general formula

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where R¹ is as defined above.

5 The 2-cyano-2-alkoxyacetamide (III) may be isolated or the dehydration reaction can be continued until the reaction product of the formula I is obtained.

10 To isolate the 2-cyano-2-alkoxyacetamide (III), the progress of the dehydration reaction is followed, for example by means of thin layer chromatography. The reaction is stopped at a suitable time, for example by cooling the boiling reaction mixture to 50-0 °C, preferably to about 0 °C.

The workup is effected by known methods, for example by means of extraction in the presence of a base and subsequent chromatography. An example of a useful base is sodium hydrogencarbonate.

15 The compounds of the formula III are chiral. They may be either in the S-configuration or the R-configuration. The above-described dehydration results in the racemate which may be separated into the two isomers by known processes, for example by HPLC chromatography using a column having a chiral stationary phase. Chiral stationary phases are known and commercially
20 available, for example from E. Merck, Waters, Daicel or Macherey & Nagel.

The compounds of the formula III are novel and likewise form part of the subject-matter of the invention.

25 The compounds of the formula III can be converted in a similar manner to 2-cyanoacetamide, for example using 2-mercaptobenzoic acid to prepare 2-(4-oxobenzothiazin-2-yl)acetamide (N. S. Ibrahim et al., *Heterocycles* 1984, 22(8), 1677-1682), using 1,2-diaminobenzene to prepare benzimidazol-2-yl-acetonitrile (T. A. Fairley et al., *J. Med. Chem.* 1993, 36(12), 1746-1753) or
30 using 2-cyanothioacetamide to prepare thiopyridines (R. M. Mohareb et al., *Z. Naturforsch. B. Anorg. Chem. Org. Chem.* 1986, 41(1), 105-109). Equally, the compounds of the formula III are useful for preparing barbiturates, coumarins or vitamins in a similar manner to the known use of 2-cyanoacetamide.

35 The examples hereinbelow illustrate the process according to the invention.

Example 1

Preparation of methoxymalononitrile in the presence of POCl₃

13.62 g (87.0 mmol) of POCl_3 and 0.3 g (2.3 mmol) of AlCl_3 were added to a solution of 10.0 g (75.7 mmol) of methoxymalonamide in 50 ml of acetonitrile and the reaction mixture was heated to reflux for 4 h. The solvent was distilled off, water was added and the aqueous phase extracted using diethyl ether (3×50 ml). The organic phase was dried and the solvent taken off on a rotary evaporator. Purification of the residue (7.28 g) by means of Kugelrohr distillation (110 °C/20 mbar) delivered 4.42 g (61%) of methoxymalononitrile as a colorless liquid.

^1H NMR (CDCl_3): δ = 5.26 (s, 1H); 3.65 (s, 3H).
 ^{13}C NMR (CDCl_3): δ = 110.12 ($\text{C}\equiv\text{N}$); 57.58 (CH_3); 57.33 (CH).

Example 2

Preparation of methoxymalononitrile in the presence of trifluoroacetic anhydride

In a 250 ml round-bottom 3-neck flask, 10 g (75.7 mmol) of methoxymalonamide, 22 g (278 mmol) of pyridine and 100 ml of dioxane were initially charged under argon. At 2-5 °C, 48.3 g (230 mmol) of trifluoroacetic anhydride were added dropwise. The reaction mixture was allowed to react at room temperature for 24 h. Afterwards, 200 ml of water and then 200 ml of methylene chloride were added at 10 °C. After the phase separation, extraction was effected once more using 200 ml of methylene chloride. The combined organic phases were concentrated, and the resulting oily crude product (7 g) was distilled (27-30 °C/1.6 mbar).

Yield: 2.6 g; 33%

Example 3

2-Cyano-2-methoxyacetamide

6.74 g (44 mmol) of POCl_3 and 152 mg (1.14 mmol) of AlCl_3 were added to a solution of 5.0 g (38 mmol) of methoxymalonamide in 100 ml of acetonitrile at room temperature. This mixture was then heated to boiling under reflux and the progress of the reaction was followed by means of TLC (eluent: ethyl acetate/hexane 1/1; R_f of the product: 0.24). After 2.5 h, the reaction mixture was cooled to 0 °C and poured cautiously with stirring into a 100 ml of a saturated sodium hydrogencarbonate solution. This mixture was then extracted 5 times with 100 ml of ethyl acetate each time. The combined organic phases were dried over Na_2SO_4 and concentrated by evaporation. Subsequent flash

chromatography using Si60 silica gel (column 25×5.5 cm; hexane/ethyl acetate 3/1) gave 3.5 g (81%) of 2-cyano-2-methoxyacetamide as a colorless liquid which solidified on cooling.

¹H NMR (CDCl₃): δ = 6.85 (bs, 1H); 6.65 (bs, 1H); 4.65 (s, 1H); 3.63 (s, 3H).

¹³C NMR (CDCl₃): δ = 165.2 (C=O); 114.2 (C≡N); 70.6(CH); 58.7 (CH₃).